REMARKS

Support for the recital of measuring a therapeutic activity is provided at e.g., p. 19, lines 13-15 and p. 65, lines 10-13. New claims 39 and 40 recite elements in parallel with claims 38 and 38 but do not require two teleosts per well. Claim 41 is essentially the same as claim 31 except it does not recite detecting a therapeutic activity and instead further defines the means by which the agent is contacted with the teleost. Support for the claim is provided by e.g., p. 79, line 17. No amendment should be construed as acquiescence in any ground of rejection.

Priority

Because the issue of priority does not currently appear to be material to the grounds of rejection raised, applicants will not further address this issue at this time. Applicants reserve the right to revisit this issue should it become relevant in this or subsequent proceedings.

Rejections under 112, first paragraph

Claims 31, 33 and 35-38 stand rejected under 35 USC 112, first paragraph based on the allegation that the specification does not enable screening for any desired activity. The Examiner alleges that the sections of the applications cited for support relate to screening for toxicity a drug known to have a therapeutic effect as distinct from screening for both the toxic effect and the therapeutic effect. The Examiner also alleges that the specification that the claims are drawn to use of a wildtype teleosts and it would not have been possible to screen for a therapeutic effect in a wildtype teleost. The Examiner also alleges that one would not know how to carry out the last step of assessing a desired effect. This rejection is respectfully traversed particularly insofar as it might be applied to the amended claims.

As noted above, the previous recitation of a "desired" effect has been replaced with a "therapeutic activity." The present specification provides both generic support and representative examples of screening a compound for such an activity.

Generic disclosure for concomitant screening for a therapeutic activity and a toxic activity is provided at e.g., p. 19, lines 13-15, and at p. 65 lines 10-13. Moreover, two examples

of therapeutic activities for which compounds can be screened, namely angiogenesis and apoptosis, are described in detail and exemplified in the application. Although modulation of angiogenesis can be assessed in a wildtype teleost and modulation of apoptosis in a wildtype teleost treated with retinoic acid, as exemplified, in the specification, neither the claims or specification are limited to using a wildtype teleost. The specification also refers to mutant teleosts serving as models of genetic deficiencies (p. 19, lines 16-24) and transgenic teleosts serving as models of e.g., cancer (e.g., p. 15, lines 27-30). It is of course well-known that higher forms of animals, such as mouse, can be used as models of a variety of human diseases by techniques such as mutation, transgenesis or chemical induction. Given the generic teaching of the specification regarding use of teleosts for assessing therapeutic potential of compounds, the detailed description of two representative examples of such assays, as well as disclosure of alternative transgenic and mutagenic approaches, in conjunction with common knowledge in the art regarding general principles of using higher animals as models of disease, it is respectfully submitted that the artisan would have been able to screen compounds for a variety of therapeutic activities in teleosts without undue experimentation.

Rejections under 112, second paragraph

Claim 31 stands rejected on the basis that it is not clear whether the reference to detecting a change *in vitro* or *in situ* means that the detection occurs *in vitro* or *in situ* or the change occurs *in vitro* or *in situ*. In reply, the *in vitro* or *in situ* was meant to qualify the detection. The claim has been amended for greater clarity.

The Examiner also alleges that reference to "the teleost" in line 7 of claim 31 is unclear as to which teleost is being referred to. Applicants are referring to the teleost to which the agent has been administered. The claim has been amended for improved clarity.

Claim 33 stands rejected for reciting "the response," which is alleged to lack antecedent basis. In response, the "response" has been changed to the "change" for improved antecedent basis.

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Rejection under 35 USC 102(b)

Claims 31, 33 and 35 stand rejected over Mizell. The rejection is maintained because the Examiner's construes the previous recitation of a desired activity as not excluding a toxic activity. It is respectfully submitted that such concerns are moot in view of the amendment of the claims to recite that the agent is screened for a therapeutic activity.

Rejection under 35 USC 103

Claims 36-38 stand rejected over Mizell in combination with Terse. Mizell is applied as above. Terse is alleged to teach using a microwell plate. This rejection is respectfully traversed. First, Terse does nothing to compensate for Mizell's lack of teaching of screening for a therapeutic activity. Second, applicants disagree that it would have been obvious to combine the references. Although microwells are very commonly used for performing various biochemical assays of the type discussed by Terse, no reference has been identified as using microwells for culturing a living organism. The issue in using such a microwell for culturing a living organism is not simply that the living organism be able to fit within the well but that the resulting confinement in combination with possible accumulation of waste products, and possible lack of aeration would cause abnormal development or death of the organism frustrating the purpose of the assay. It is common experience to owners of pet fish that issues such as oxygenation, removal of waste products and nutrition can be of critical important to a fish's wellbeing and survival even in much larger tanks. Consistent with such concerns, Mizell used Petri dishes as a vessel to contain zebrafish and previous work reviewed by Mizell also apparently used large volumes as judged by the 18 liters of waste water reported at p. 412, second column, second paragraph. For these reasons, it is respectfully submitted that it cannot simply be assumed that the skilled person would have found it obvious to perform the claimed methods in the wells of microtiter plates absent any teaching in the scientific literature that such plates had ever been used to culture a living fish.

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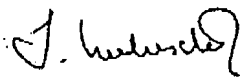
New claim 39 is distinguished by the recital that the agent is added to culture media containing the teleost and permeates the teleost. Mizell uses microinjection into the perivetelline space (see p. 414). Mizell also notes that adding toxic compounds to the culture media was unsatisfactory because only at very high concentrations did deleterious occur and such experiments generated large volumes of contaminated water causing disposal problems (p. 412). Thus, Mizell would have taught away from adding agents to culture media to assess toxicity of an agent by measuring changes of a protein or mRNA in a specific organ or tissue.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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